

Review

# Surfactant Metabolism Dysfunction and Childhood Interstitial Lung Disease (chILD)

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## SUMMARY

Surfactant deficiency and the resultant respiratory distress syndrome (RDS) seen in preterm infants is a major cause of respiratory morbidity in this population. Until recently, the contribution of surfactant to respiratory morbidity in infancy was limited to the neonatal period. It is now recognised that inborn errors of surfactant metabolism leading to surfactant dysfunction account for around 10% of childhood interstitial lung disease (chILD). These abnormalities can be detected by blood sampling for mutation analysis, thereby avoiding the need for lung biopsy in some children with chILD.

**Key Words:** Surfactant, child, mutation analysis.

## INTRODUCTION

The role of surfactant deficiency in the development of RDS in preterm infants has long been appreciated and surfactant replacement is now a well established treatment modality. Term infants can also present with the clinical picture of RDS as a result of surfactant inactivation, secondary to conditions such as meconium aspiration or congenital pneumonia. However, it is less well known that inborn errors of surfactant metabolism leading to surfactant dysfunction are now thought to be an important cause of childhood interstitial lung disease.

## chILD

Childhood interstitial lung disease (chILD) is much rarer than interstitial lung disease (ILD) in adults and is typically associated with respiratory distress, diffuse infiltrates on chest imaging and abnormal lung histology. ChILD, like ILD in adults, comprises a spectrum of heterogeneous disorders. Until recently these have been poorly described, with the relevant literature consisting of case reports and small case series only. Previous attempts to classify chILD on the basis of the lung histology have used adult classifications, but it is now recognised that the histology and associated clinical outcome seen in children, especially those under 2 years, differs significantly from that of adults. Common histopathological findings of ILD in adults include desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP) and usual interstitial pneumonia (UIP). UIP has not been reported in any paediatric cases to date. Although some overlap in histology does occur, for example with DIP, chILD is associated with a different aetiology compared to adults. This further emphasises that the adult classification of ILD is of little benefit in defining ILD in children. A recent review of 187 open lung biopsies in young children has identified

pathology largely unique to children presenting in infancy, the majority presenting as either a term baby with features of RDS or with 'chronic tachypnoea of infancy'. The underlying histology, clinical course and resultant prognosis have been described<sup>1</sup> and are summarized in Table I.

The overall mortality associated with chILD is 21%<sup>2</sup>, but almost all deaths occur in those with developmental lung disorders and some of the surfactant deficiencies. In contrast, infants with pulmonary interstitial glycogenosis (PIG) or neuroendocrine cell hyperplasia of infancy (NEHI) often demonstrate significant clinical improvement over time. Although the presentation of these disorders is often similar, the age at presentation offers an important clue to the underlying diagnosis and subsequent prognosis. Children under two years with ILD present either in the neonatal period or in early infancy.

## NEWBORN WITH chILD

This is commonly a term infant who presents shortly after birth with severe parenchymal lung disease causing respiratory distress and oxygen requirement. Both the clinical presentation and the radiological features of diffuse ground glass opacities are similar to those more typically seen with prematurity and surfactant deficiency. Differential diagnoses such as pneumonia or meconium aspiration syndrome, leading to transient surfactant inactivation, must be excluded. Despite intensive respiratory support with mechanical ventilation, inhaled nitric oxide or ECMO, this presentation is almost invariably fatal. The types of chILD associated with such an early and aggressive course include disorders of lung development (alveolar dysplasia and alveolar capillary dysplasia) and two of the surfactant dysfunction disorders (surfactant protein B deficiency and ABCA3 gene mutations - although the latter may also have a less severe clinical course). PIG can also present perinatally but has a much more favourable outcome relative to the other causes, with very low reported mortality.

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TABLE I:  
*Classification of interstitial lung disease in children less than 2 years*

Disorders	Prevalence
<b>Primary Disorders of Lung Development</b> (Aberration in primary molecular mechanism of lung and/or pulmonary vascular development)	5.8%
<b>Lung Growth Abnormality</b> (Impaired pre or post natal alveolarisation, largely secondary)	24.6%
<b>Pulmonary Interstitial Glycogenosis (PIG)</b>	3.2%
<b>Neuroendocrine cell hyperplasia of infancy (NEHI)</b>	9.6%
<b>Surfactant Dysfunction Disorders</b>	9.6%
<b>Miscellaneous</b> (e.g. systemic disease processes, immunocompromised states)	35.5%
<b>Unable to classify</b>	11.7%

INFANT WITH chILD

This group of children with ILD present with ‘chronic tachypnoea of infancy’, usually in the first few months of life. Clinically this is characterised by persistent tachypnoea, hypoxia, crackles and intercostal recession. The ongoing oxygen requirement and increased work of breathing cause failure to thrive. Important differential diagnoses in these children are cystic fibrosis, aspiration and immunodeficiency with recurrent infection. These must be excluded before chILD is considered. A number of conditions can give rise to chILD in infancy and include PIG, NEHI, surfactant protein C deficiency and less commonly ABCA3 gene mutations. The majority of the infants with these diagnoses experience clinical resolution over time.

The ability to define chILD using both the clinical picture and lung histology, is an extremely important development as it ensures that the most appropriate treatment and counselling are offered to children and their families. However, the recent development that surfactant dysfunction disorders underlie up to 10% of chILD may avoid the need for lung biopsy with its associated potential risks, as these conditions can be identified by genetic testing.

SURFACTANT DYSFUNCTION DISORDERS

Pulmonary Surfactant

Pulmonary surfactant is a complex mixture of phospholipids and proteins, with surfactant proteins A, B and C constituting 10% of surfactant. It is secreted by type II epithelial cells into the airways of the lung from 24 weeks gestation, although only in adequate amounts from 35 weeks gestation. Its main role is to reduce surface tension in the alveoli following the onset of breathing thereby facilitating lung expansion and preventing alveolar collapse during expiration. Following birth, mechanical stretch of the lung further contributes to the secretion of lamellar bodies, the intracellular storage granules of surfactant, which unravel to form extended tubes and sheets characterised by the formation of tubular myelin. Both surfactant proteins A and B and surfactant lipids are necessary for the formation of tubular myelin. The surfactant forms a film at the alveoli-air interface, which is respread after each expiration to maintain a low surface tension and prevent lung collapse. The spreading and stability of the surfactant film requires SP-B and SP-C. Following secretion, both surfactant proteins and lipids are recycled by the respiratory epithelium. As well as reducing surface tension, surfactant also plays a role in the innate host defence of the lung. Surfactant protein

TABLE II:  
*Surfactant metabolism dysfunction 1,2 and 3 genes.*

Gene	Type 1 (SFTP-B)	Type 2 (SFTP- C)	Type 3 (ABCA3)
<b>MIM numbers</b>	265120, 178640	610913, 178620	610921, 601615
<b>Inheritance</b>	Autosomal recessive	Autosomal dominant, sporadic	Autosomal recessive
<b>Chromosome</b>	2p12-11.2	8p21	16p13.3
<b>Clinical features</b>	Neonatal respiratory failure and death	Infantile and older chILD with respiratory failure	Neonatal and early infantile respiratory failure. Some cases reported of older children with similar pattern to adult DIP
<b>Lung histology</b>	Alveolar type II cell hyperplasia and alveolar proteinosis, interstitial inflammation and fibrosis	Variety of patterns including DIP, UIP, non-specific interstitial pneumonitis	Alveolar type II cell hyperplasia, accumulation of macrophages and proteinaceous material in airspaces

A and D primarily exert their effect in this area and are not necessary for the other functions of surfactant. ABCA3 is present in the membranes of the lamellar bodies in type II alveolar cells, where its main function is the transport of lipids important for surfactant.

It is now known that surfactant proteins B, C and ABCA3 are necessary for surfactant homeostasis and mutations in the genes encoding these proteins leads to surfactant dysfunction, giving rise to both lethal and chronic respiratory disease in infants (table II).

### Surfactant Protein B

Surfactant protein B deficiency is invariably fatal within the first few months of life. It is an autosomal recessive condition, most commonly due to a mutation at 121ins2. Gene frequency of this mutation is estimated to be between 1 in 1000 to 1 in 3000<sup>3</sup>. Infants present soon after birth with both clinical and radiological features of respiratory distress syndrome, which has a rapidly progressive course. This is refractory to standard therapies such as surfactant replacement and assisted ventilation, with the only effective treatment being a lung transplant. Lung histology shows pulmonary alveolar proteinosis (PAP).

### Surfactant Protein C

Surfactant protein C is encoded by the SFTPC gene on chromosome 8. Inherited surfactant protein C deficiency is a rare cause of both acute and chronic lung disease in both infants, children and into adulthood. Infants usually present with interstitial lung disease that may be exacerbated by respiratory infections. Histologically the condition is characterised by chronic pneumonitis of infancy (CPI) or non-specific interstitial pneumonitis (NSIP)<sup>4</sup>. As with some other surfactant deficiencies, the only effective management is lung transplantation. Definitive diagnosis is made by genetic testing to identify the SFTPC gene.

### Surfactant Protein ABCA3

ABCA3 is an ATP-binding transporter of lipids found in the membrane of lamellar bodies in type II alveolar cells. Initially mutations in this gene were thought to cause fatal lung disease in term neonates, but it is now recognised as a cause of chronic interstitial lung disease in older patients. One study looking at nine children with surfactant protein ABCA3 mutations found that the range of presentation in these children varied from birth to four years<sup>5</sup>. Clinical features found included cough, crackles, clubbing and failure to thrive. Histopathological findings from lung biopsy were variable and

included pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonitis (DIP) and non-specific interstitial pneumonitis (NSIP). In one cohort of eight patients, three had lung transplantation and a further five children who did not require transplant had survived up to 18 years at the time of publication. Although some children clearly have a milder course, this mutation can cause severe respiratory insufficiency leading to death<sup>6</sup>.

### CONCLUSIONS

chILD represents a varied group of disorders which are difficult to distinguish on clinical presentation and examination alone. The importance of obtaining an accurate diagnosis cannot be overstated as there is considerable disparity between the morbidity and mortality of these disorders. In the past, lung biopsy has been the only useful investigation and the diagnostic gold standard despite the potential complications associated with it. However, the identification of the genes responsible for surfactant dysfunction disorders avoids the need for a biopsy in approximately 10% of children. We therefore suggest that blood sampling for gene analysis be offered to all infants presenting with 'chronic tachypnoea of infancy' as the initial investigation and that lung biopsy is considered only if gene analysis is normal.

Conflict of interest: the authors have no conflict of interest to declare.

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